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Bone Lead, Hypertension, and Lead Nephropathy

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There is considerable clinical evidence that excessive lead absorption causes renal failure with hypertension and predisposes individuals to hypertension even in the absence of detectable renal failure. Recent analyses of transiliac bone biopsies indicate that unsuspected elevated bone leads may reflect the cause (or contributing cause) of end-stage renal disease in 5% of the European dialysis population. In these patients, bone lead levels were four times higher than in unexposed cadavers (6 μg/g wet weight) and approximated levels found in lead workers (30 μg/g). At present, the most reliable index of the body lead burden is the $CaNa_2$ EDTA lead mobilization test. *In vivo* tibial X-ray-induced X-ray fluorescence (XRF) is a more practical noninvasive technique for assessing bone lead, which should find widespread application as a diagnostic tool and for epidemiologic studies.

Exposure Levels in Adults

The role of environmental lead in the induction of hypertension and renal disease in adults has received little attention since measurements in the nineteenth century first suggested a relationship between lead, high blood pressure, and disease of the kidneys (*1*). There is now considerable evidence that excessive lead absorption causes slowly progressive renal disease and that lead predisposes individuals to hypertension even in the absence of detectable renal failure.

The health effects of lead in adults has gone largely unrecognized because of conventional reliance on the blood lead measurement (PbB) using criteria for normal based on symptomatic acute poisoning. Over 90% of the body burden of lead is stored in bone and has a biological half-life approximating several decades (*2*). Cumulative lead absorption is best assessed at present by the EDTA lead mobilization test (*3*). The chelation test correlates well with bone lead concentrations determined by direct measurement and thus provides a good estimate of the body lead burden.

It is useful to consider the health consequences of lead in four, often overlapping, exposure categories (Table 1).

Classical Acute Lead Intoxication

Massive lead absorption over a brief period of time induces abdominal colic, peripheral neuropathy, mental dysfunction, seizures, and anemia. These symptoms of acute poisoning have been recognized for 2000 years. In adult lead workers, transient hypertension is common during the acute phase. In children, the kidneys leak amino acids and other circulating substances normally reabsorbed by the proximal tubule (Fanconi syndrome). Blood lead levels are more than 70 μg/dL during the acute episode. Symptoms are reversed by chelation therapy or termination of exposure.

Chronic Industrial Exposure

Continuous lead absorption at levels insufficient to produce the hallmarks of acute intoxication, increases the body burden of lead and can induce hypertension, interstitial nephritis, and behavioral abnormalities after a few years. Blood lead levels depend on the proximity to recent exposure and may be only modestly elevated at the time clinical symptoms are recognized; PbB is from 30 to 80 μg/dL. Nonoccupationally exposed adult males have mean PbB levels of about 15 μg/dL (*4*). Prolonged exposure in the workplace produces bone lead stores that are more than four times that of nonoccupationally exposed individuals. Transiliac bone biopsy lead levels averaged 30 μg/g in 22 Belgian lead workers (*5*). The mean chelatable lead in these men was 1923 μg/3 days. In individuals without unusual exposure, transiliac bone lead levels averaged 6 μg/g.

Sporadic Exposure

Increased total body lead burdens result from intermittent (usually unrecognized) exposure in the absence of symptoms of acute intoxication. Sporadic high

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Table 1. Levels of lead exposure.

Type of exposure	Description	Source	Symptoms	Blood lead, μg/dL	Iliac [Pb], μg/g
Acute	Massive Rapid	Pica Fumes Accident Moonshine	Seizures Neuropathy Mental Fanconi syndrome Transient hypertension	70–200	Time dependent
Chronic	High Persistent	Workplace	Hypertension Renal Mental	30–80	> 25
Sporadic	Moderate Occasional	Paint Glazes Workplace Moonshine Water	Hypertension Renal Mental	20–50	> 20
Ambient	Low Persistent	Gas Water Food	Hypertension IQ	10–25	5

exposure derives from occasional work situations; from contaminated food, water, or alcoholic drinks; from the dust of old paint chips; and the leaching of lead from improperly prepared glazes. It has recently been found that dangerous quantities of lead can leach through unleaded glazes from painted surface decorations on ceramic (Donald M. Wallace, personal communication). Sporadic high lead absorption may cause body burdens to increase to levels seen in lead workers after 1 to 5 years. Transiliac lead levels exceed 20 μg/g and the PbB is 20 to 50 μg/dL. The frequency of sporadic exposure may approach 1%, approximating the frequency of blood lead levels over 30 μg/dL in the general population (*4*).

Ambient Lead Exposure

This is the ubiquitous lead exposure that most of the world encounters. The effect of normal lead absorption on blood pressure is the subject of other papers in this meeting. Universal exposure makes it difficult to identify appropriate control groups. Consequently, the generally accepted upper limit of normal for the EDTA lead mobilization test (650 μg lead chelate/day) is undoubtedly too high. Clinical studies of small groups to detect the role of lead in hypertension are, therefore, likely to be unproductive.

It is the third level, sporadic and unrecognized lead exposure, that we have studied over the last 7 years. None of these patients was aware of excessive past lead absorption. None had suffered the symptoms of acute lead intoxication and none had a diagnosis of lead nephropathy prior to these studies.

Body lead burdens were assessed with the EDTA lead mobilization test in 21 hypertensives with renal failure (serum creatinine > 1.5 mg/dL), 27 hypertensives without renal failure, and in 22 patients with renal failure not due to lead (*6*). The chelation test was performed by giving 1 g $CaNa_2EDTA$ IM twice, 12 hr apart, and collecting urine for measurement of lead chelate and creatinine excretion for the subsequent 3 days. To each 5 mL of EDTA, 1 mL of 2% lidocaine was added. The mean chelatable lead in the patients with hypertension and renal failure was significantly higher than that of hypertensives without renal failure, 860 ± 30 versus 340 ± 39 μg Pb/3 days, respectively (Table 2). Chelatable lead was also higher in hypertensives with renal failure than in control patients with comparably diminished renal function due to another identifiable etiology (440 ± 50 μg/3 days). The control renal failure group demonstrates that renal failure *per se* does not increase mobilizable lead. Moreover, the known duration of hypertension in the patients with renal failure (7 years) was half of that of hypertensives with preserved renal function (14 years). The in-

Table 2. Patients with essential hypertension.[a]

Category	No. of patients	Age, years	Serum creatinine, mg/dL	Urinary protein, mg/day	Blood lead, μg/dL	EDTA test results, μg Pb/3 days
No renal disease	21	55 ± 2	1.2 ± 0.1	257 ± 67	18 ± 2	340 ± 39
Renal disease	27	57 ± 2	3.2 ± 0.5	642 ± 133	19 ± 4	860 ± 10
p value		NS[b]	< 0.001	< 0.001	NS	< 0.001
Renal controls[c]	22	54 ± 3	3.4 ± 0.5	1971 ± 779	15 ± 2	440 ± 50

[a]Values expressed as mean ± SEM.
[b]NS, not significant.
[c]Renal controls were patients with renal failure of nonlead causes.

creased duration of elevated pressure in patients without renal failure indicates that hypertension was not the cause, but the result of renal disease. Although these patients had been considered to have essential hypertension prior to chelation testing, the study indicates that lead played an etiologic role in the development of hypertension and renal failure in some.

This interpretation is founded on the assumption that the accessibility of bone lead stores to the chelating agent is essentially equivalent in hypertensive and control renal failure patients. Studies recently performed in DeBroe's laboratory at the University of Antwerp support this view (*5*). One hundred fifty-three transiliac bone biopsies obtained for aluminum studies from patients with end-stage renal disease were analyzed for lead and calcium. The mean bone lead in these dialysis patients was 6 μg/g, indicating that bone lead is not elevated by end-stage renal disease and that the increased mobilizable lead in hypertensives with renal failure is, therefore, not due to increased lead storage induced by renal failure. Moreover, patients with analgesic nephropathy, a form of interstitial nephritis that can be accurately diagnosed, had low levels of iliac lead (mean = 4 μg/g). Interstitial nephritis therefore does not appear to induce a unique form of uremic osteodystrophy characterized by increased bone lead stores.

Five percent of the French, German, and Belgium dialysis patients studied in Belgium had iliac bone lead levels comparable to those found in lead workers: 20 μg/g wet weight. Bone histomorphometry in the dialysis patients with elevated bone leads did not differ from that in dialysis patients with low bone leads confirming the absence of unique bone disease. These data suggest that up to 5% of the European dialysis population have unsuspected excessive lead absorption as the cause, or contributing cause, of their end-stage renal disease (*5*).

Additional studies of 24 Belgian lead workers demonstrated that the chelation test provides a good estimate of bone lead. The lead content of transiliac bone biopsies compared to the EDTA lead mobilization test gave a linear regression correlation coefficient (r) of 0.87. Taken together, these studies provide criteria for the diagnosis of excessive cumulative lead absorption directly from bone biopsies, which may prove useful in functionally anephric patients.

Evidence was also obtained in Antwerp indicating that measurement of the Pb:Ca ratio in bone is more reliable than the absolute bone lead concentration. Bone Pb:Ca shows less variability than the [Pb], presumably because of the variable quantity of noncortical bone in the biopsy specimens. In addition, the effect of demineralization due to uremic osteodystrophy is minimized when the Pb:Ca ratio is used.

The Pb:Ca ratio has another advantage. It is precisely Pb:Ca that is most accurately measured by the new technique of *in vivo* tibial X-ray induced X-ray fluorescence (XRF) using characteristic K X-rays from lead, elicited by a ^{109}Cd radioactive source (*7,8*). This technique for assessing bone lead content eliminates the need for injecting EDTA and for urine collections and thus is a more practical diagnostic tool particularly for epidemiologic studies. The main limitation of XRF using K fluorescent X-rays may be the difficulty in measuring bone lead levels encountered in the normal population (< 10 μg/g). XRF can detect bone lead levels of 20 μg/g or higher with good precision and therefore is suitable for detecting individuals at risk from industrial level lead absorption.

In 21 unselected renal patients from New Jersey tibial lead (determined by *in vivo* XRF) and chelatable lead levels fell within the expected range (95% confidence limits) found by direct transiliac bone biopsy in the 24 patients from Antwerp who had EDTA lead mobilization tests (Fig. 1). XRF therefore appears to be suitable for determining the risk of renal disease in the general population and in dialysis patients, an undertaking that is essential for public health planning.

These studies provide insight into the question: How much lead is too much? The normal population has an iliac lead concentration of about 5 μg/g compared to > 20 μg/g in lead workers. A fourfold increased in bone lead in occupational as compared to ambient exposure has also been reported by Barry (*3*). Thus, a fourfold increase in lead absorption places an individual at the same risk as the lead worker for lead-induced hypertension, renal disease, and behavioral abnormalities. The total body lead of a 70-year-old man (whose bone lead is 5 μg/g) approximates 200 mg (*9,10*). Consequently, the absorption of 500 μg excess Pb per day for 5 years (182 mg/year) turns a normal body lead burden into that of an industrial lead worker. Such absorption can easily be acquired from lead leached from ceramics, from contaminated water, or from pulverized old lead paint chips. Current FDA regulations permit 5 ppm to be leached from ceramics. This would provide enough

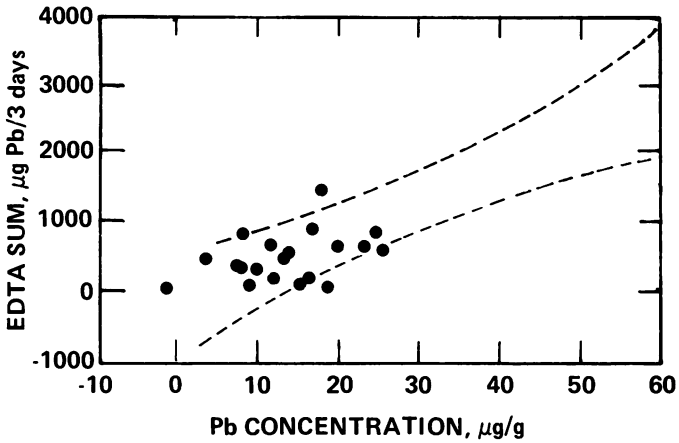

FIGURE 1. *In vivo* tibial XRF [Pb] and chelatable Pb (EDTA test) in 21 New Jersey VA patients (•) plotted within 95% confidence limits of 24 Belgian patients (including lead workers) in whom bone lead was measured by atomic absorption spectroscopy from transiliac biopsies. (Iliac lead conversion factor to tibial lead = 1.7.)

lead to reach the usual adult maximum body burden in 1 year. Individuals who consume 1 L a day of liquid containing 5 ppm Pb would accumulate almost 200 mg Pb a year, assuming 10% absorption. The risks to adults of sporadic high lead absorption from such unrecognized sources must be addressed by the medical, public health, and lead manufacturing communities.

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